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Potentials for Progress in Laser Medicine

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Lasers could come to occupy a highly important position in the armament of medicine. They are the brightest known sources of light, man-made or natural, and emit light having such properties as coherence and monochromaticity. Furthermore, lasers have the ability to deliver very brief pulses of light which can cause unique alterations in biological materials. The major obstacle to the increased use of lasers in medicine and surgery is not the availability of laser devices, but the dearth of basic information about laser-tissue interactions.

We have recently demonstrated that, even in turbid tissue such as the dermis, it is possible simultaneously to induce microscopically selective thermal damage, localized to millions of selectively absorbing targets, while sparing surrounding tissues. These "targets" may be as small as organelles or as large as blood vessels. Such localized thermal damage is truly unique to pulsed laser exposures. The scope and medical utility of these lesions has yet to be fully understood.

Thus, there is much research to be done in describing and characterizing laser-induced injury. There is, however, ample evidence that several laser therapies could be improved by using selectively absorbed, short pulses that lead to the spatial confinement of thermal injury. Treatment of port wine stains, pigmented lesions, atheromatous arterial plaques, and the fragmentation of kidney and gall stones are examples. It should also be possible to use a variety of systems to deliver exogenous laser targets on or within individual types of cells or organelles. Such chromophores may lead to new forms of cancer therapy, for example.

INTRODUCTION

In the next few years, lasers will alter the practice of surgery and medicine; the impact could be enormous. Surgical procedures will continue to become less invasive, as it will no longer be necessary to create surgical openings large enough to accommodate bulky instruments and hands. The access route to the surgical field can be the size of the fiber optic threads used to carry the light that will then cut, seal, and remove tissue. Other surgical procedures may be done without any cutting or anesthesia at all. Just as the physician can see, via the endoscope, to obtain valuable diagnostic information, the laser can send high-intensity light via the endoscope for therapeutic purposes.

What may be some of the effects on patient care and the practice of medicine? Operating room procedures may in part be replaced by endoscopic suite procedures. Thus inpatient care will be replaced by outpatient procedures. The chronic GI bleeder, for example, with a hereditary vascular lesion may be safely, less invasively, and more effectively treated on a frequent basis, thus decreasing blood loss and removing the need for lengthy surgical procedures with high rates of morbidity and mortality. The judgment, approach, decisions, and referral system of physicians may be altered by laser treatments. For example, the dysphagia of end-stage esophageal cancer can now

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be palliatively treated with either a nonrepeatable operating room procedure requiring general anesthesia, or repeatedly and less invasively using an argon or Nd:YAG laser. The cost of some laser treatments may be less than traditional treatments of the past. If chosen carefully, a single laser system costing between $20,000 and $70,000 can potentially be used for many procedures on many patients. Lengthy, expensive, inpatient surgical procedures may be replaced by less expensive, outpatient laser treatments—and perhaps most important, laser treatment may improve patient care.

To date, the largest impact of lasers has been in the specialty of ophthalmology. Retinal detachment and bleeding are now routinely treated with lasers. One of the largest efforts in all of laser medicine research, however, is aimed at the treatment of large-vessel pathology via catheters (e.g., laser angioplasty). Other research has shown that the potential use of lasers in otolaryngology, gynecology, neurosurgery, cardiology, urology, plastic surgery, dermatology, and gastroenterology far exceeds the present applications.

To describe laser therapy in its simplest form, one could state: "Lasers can quickly put a lot of energy into a very small volume of tissue." This energy causes a photophysical event similar in many respects to other, well-studied, laser materials-processing events. Thermally, lasers can cook, cut, ablate, seal, and explode the tissue. The host response to this intervention, however, is unique because the laser energy can be confined to a remarkably small volume (on the order of organelles) and can be deposited in a time-frame faster than ever occurs in nature (e.g., one microsecond). Lasers, with endoscopic delivery systems, can also be used to initiate photochemically mediated reactions in tissues previously not available for light exposure such as vessels, the bronchial tree, the gastrointestinal tract, the genitourinary system, the biliary tree, and the peritoneal and thoracic cavities.

Two scientific and technical fields have converged to increase markedly the capabilities of laser medicine. First, laser technology has advanced, primarily in response to the needs of the materials-processing industry, which was supported by massive investments by the defense and communications industries. The result has been new lasers capable of tunable wavelengths, extremely brief pulse durations, and unmatched power. Second, fiber optic technology and endoscopy have also grown rapidly. Development of flexible fiber optics is an advancement which has enabled the endoscopist to see tissues directly, and thereby to target them for laser treatment of respiratory, urinary, and gastrointestinal tracts and of other regions.

The major obstacle to increased use of lasers in medicine and surgery is the dearth of basic information about laser-tissue interactions. That small volume of information is, however, growing. In 1965, there were six scientific articles published in major medical journals about the medical applications of lasers. In 1975, there were 24, and in the one month of March 1985, there were 124 articles. Nevertheless, of the several hundred kinds of lasers developed, only four or five are commonly used in medicine.

LASER PROPERTIES

The unique therapeutic capabilities of lasers are based upon the unique physical properties inherent in laser light. The high *intensity* of the laser output is a well-known property. Peak powers as high as 10^{12} watts for Q-switched and mode-locked lasers allow a wide spectrum of phenomena to occur, from gentle heating to violent explosions. Furthermore, because the laser is a spatially coherent source, the output beam can be highly *collimated* and can be *focused* to a small spot size. A collimated

TABLE 1
A Partial Listing of the Lasers Currently Used in the Clinical and Medical Research Environments

Laser (active medium)	Wavelength (nm)[a]	Use in Medicine/Surgery
1. ArF	193	Ablation[b]
KrF	248	Ablation[b]
2. Dye	Tunable	Coagulation
	(312–1,010)	Ablation[b]
3. Argon	488	Coagulation
	514.5	Ablation[b]
4. Nd:YAG	1,064.5	Disruption, coagulation
	1,320	Ablation
5. CO_2	10,600	Ablation

[a]Note that the entire spectrum from the UVC (193 nm) to the IR-C (10,600 nm) is used.
[b]Experimental

beam can be precisely aimed at a specific target. Focusing allows one to couple the light into a fiber optic, to be delivered endoscopically to many organs in the body.

The output of lasers can be extremely *monochromatic*. Some lasers emit light at only one wavelength, others at several discrete wavelengths, and still others are tunable over a broad band (refer to Table 1). Selective absorption by tissue can lead to selective damage. For example, if a chosen wavelength is generally not well-absorbed by the laser-exposed tissue, but is well-absorbed by isolated structures (e.g., blood vessels) within the tissue, then millions of these absorbing structures can be simultaneously and selectively heated and damaged by a single pulse of light in a process referred to as selective photothermolysis [1]. In contrast, if a wavelength is chosen that is well-absorbed by tissue (for example CO_2 laser light—10.6 μm—is strongly absorbed by the water in tissue [2]), then the energy in the laser beam is deposited very near the surface of the irradiated tissue, and the surface layer of tissue can be quickly heated to the point of vaporization, leaving a well-defined crater [3,4]. This process is referred to as photoablation.

Lasers are capable of generating light in a *continuous wave* (cw) or in the form of *pulses* of light as short as 10×10^{-15} seconds in duration [5]. The pulsed nature of some lasers is the key to the spatial confinement of laser-induced heating. The laser deposits energy in an absorbing structure, thereby rapidly heating that structure. The structure then dissipates this heat, mainly by conduction, to adjacent tissues. The time required for a cylindrical structure, such as a blood vessel, to cool by the process of diffusion [6], is called the thermal relaxation time (τ_R) and is expressed by the equation:

$$\tau_R = r^2/4\alpha$$

where r is the structure's radius and α is the thermal diffusivity of tissue (approximately 10^{-3} cm^2/second) [7]. The cooling time is important because if the laser pulse is longer than the cooling time, then a significant amount of heat will diffuse out of the target during irradiation. Although selective target damage may be possible with somewhat longer pulses, damage to the target will be maximally confined if the laser pulse is shorter than the target cooling time [8,9]. For example, consider oxyhemoglobin, a chromophore (i.e., an absorber of light) with absorption peaks at 415, 542, and 577 nm [10,11]. By varying the pulse duration, one can selectively heat erythrocytes ($r \simeq 3$ μm; therefore $\tau_R \simeq 20$ μsec) or microscopic blood vessels ($r \simeq 5$–10 μm, therefore $\tau_R \simeq 60$–250 μsec) or larger blood vessels plus some perivascular tissue ($\tau_R > 250$ μsec).

The above-mentioned laser properties can be varied to control several basic laser-tissue interactions. All of these interactions are dependent upon the absorption of light by tissue. The laser thus deposits energy within the tissue. Often this energy takes the form of heat, as in photothermal ablation and selective photothermolysis; however, if the photon energy is large enough, as it may be in the ultraviolet (UV), then it is postulated that chemical bonds are broken via a non-thermal mechanism, as in ablative photodecomposition. Photothermolysis and photoablation, both thermal and non-thermal, are further discussed below. Another laser-tissue interaction called photodisruption can cause damage by photon-induced acoustic shock waves. These shock waves result from very tight focusing of laser light. Such focusing is only possible in nonscattering media such as the eye. Because photodisruption therapy is likely to be of import only in the field of ophthalmology, there will be little further discussion of that laser-tissue interaction in this paper.

PHOTOABLATION

Ablation refers to the removal of surface material. Photoablation is not a new phenomenon; it has been used in both industry [12,13] and medicine [14,15] for a long time. The mechanisms of photoablation are either entirely thermally based (as exemplified by the CO_2 laser) or based upon a process called photodecomposition (as exemplified by ultraviolet-emitting excimer lasers).

Photothermal ablation is initiated by absorption of laser light near the tissue surface; as surface temperature rises, a phase change occurs, and the tissue is vaporized, leaving a crater in the tissue surface. The depth of this crater and the amount of thermally denaturated tissue left behind depend upon laser wavelength, exposure parameters, and material properties. The major surgical advantage over cold-knife dissection is that of controlled hemostasis [14,16]; a small amount of heat remains at the edge of the ablation site to enhance blood coagulation and microvessel sealing. Advantages over electrocautery techniques are that, with a laser, one can have better control of tissue heating, depth of ablation or incision, and the amount of residual tissue thermal damage [17].

Ablative photodecomposition was discovered during the etching of polymer films by high-intensity ultraviolet laser light [18]. Ultraviolet light is now being used experimentally to cut biologic materials [19,20]. Photodecomposition is initiated by the absorption of focused UV laser radiation. It is postulated that UV photons have sufficient energy (e.g., 6.4 eV photon at 193 nm) to break bonds in a hydrocarbon chain, so that smaller, fragmented molecules are produced. The fragments rapidly fly off, leaving a shallow crater (typically <1 μm deep) in the material surface. In some cases, there is no detectable thermal damage to the material adjacent to the ablation crater [21]. Recent 248 nm studies in human and guinea pig skin, however, have shown some thermal damage to collagen and cellular structures within 100 to 200 μm of the ablative edge. Thus, for some biologic materials, a photothermal mechanism may be at least partially responsible for the ablation [20]. The proportion of thermal versus decomposition mechanisms in UV ablation is at this time uncertain [22].

The depth of the etch mark is controlled by the mechanical properties of the tissue and the laser wavelength, radiant exposure, irradiance, pulse repetition rate, spot size, pulse duration, and, for continuous wave lasers, dwell time. Generally, a small increase in radiant exposure means that more tissue receives an ablative dose of laser energy; thus the depth of the crater increases [20,21,23]. Similarly, somewhat more tissue is ablated during slightly longer pulses of equivalent irradiance [24]. Wavelength controls the depth of light penetration into the tissue and the site of absorption. A very short penetration depth (e.g., at 193 nm, the penetration depth is approximately 2.0 μm) means the light is absorbed very strongly; thus little tissue (e.g., 2.0 μm) is removed with every pulse of light. A slightly longer penetration depth (e.g., at 248 nm the penetration depth in dermis is 50–100 μm) means more tissue can be ablated per pulse. Note, however, that at a near infinite penetration depth so little light energy is absorbed that ablation is not possible.

The zone of thermal damage at the edge of the ablation crater is also controlled by the laser exposure parameters. The shorter the penetration depth, the more focal the deposition of laser energy; the more localized the confinement of heat, the smaller the zone of thermal damage [24]. Thus, the pulse duration of the laser also controls the zone of thermally altered tissue. When the tissue surface is heated, thermal diffusion controls the heating of the tissue surrounding the irradiated surface volume. If the surface volume is heated faster than it can cool (i.e., if the pulse duration is much less than the thermal relaxation time of the heated volume), the surrounding tissue is minimally heated. Furthermore, when the surface material flies off, a significant percentage of energy leaves, and little energy is left to heat the remaining tissue [19,20,21]. Laser intensity is also important. Laser pulses that lack sufficient intensity to ablate tissue simply heat the surface of the tissue and can cause thermal damage to underlying structures [25]. To minimize the zone of thermally altered tissue surrounding the ablation crater, short pulses of strongly absorbed, high-intensity light are needed. Depending upon the application, one may not want any zone of thermal damage (for example, in corneal surgery) or may want only a small zone for sealing vessels and limiting bleeding in the area adjacent to the crater (e.g., in the skin).

Although the amount of material removed per pulse is quite small, a "deep" cut can be achieved by using many pulses. The zone of thermal damage surrounding the cut can be as minimal as for one pulse. Also, although the mutagenic and carcinogenic capabilities of ultraviolet radiation are well known, most of the tissue irradiated by the UV light is ablated; little tissue receiving a sub-ablative dose is left intact. In addition, recent studies, while confirming the cytotoxic and mutagenic potential of 248 nm laser radiation, have shown that 193 nm radiation was cytotoxic but not very mutagenic when compared with controls. At 193 nm, the nucleus, and therefore the DNA, appears to be effectively shielded by strongly absorbing perinuclear components [26].

The UV laser ablation of corneal tissue [19] may help perfect the correction of myopia by radial keratomy [27,28]. The advantage of using the UV laser as opposed to a diamond knife are that the laser may offer better control over the depth and positioning of the cuts, and there is perhaps less chance of an adverse host response because there is very little damage to the tissue adjacent to the cut [29].

Lasers used in an ablation mode may also provide an effective means of removing atherosclerotic plaque. The ultimate goal is quite clear: the removal of plaque in such a manner that normal vessel structure is unaltered and the atherosclerotic lesion does not reform [30]. It has been shown that fibrous plaque absorbs twice as strongly between

420 and 530 nm as normal aortic wall. Carotenoids, known components of plaque, also absorb strongly in this region. Thus, oral administration of carotenoids may further enhance the selective absorption of plaque, providing a spectral region in which plaque can be selectively ablated [31].

PHOTOTHERMOLYSIS

Photothermolysis refers to the light-induced heating of selectively absorbing targets [1]. The basic elements for achieving this are: *(1)* selective absorption of the incident light by the pigmented "target" structures within otherwise relatively nonabsorbing tissue, and *(2)* confinement of the resultant heat generated within these target structures. Irreversible denaturation of the targets then becomes possible. Thus, photothermolysis is dependent upon a light source that: *(a)* is intense, so that rapid heating can be achieved; *(b)* emits light at a wavelength that is well-absorbed by the selected target but relatively poorly absorbed by the surrounding tissue; and *(c)* is pulsed, or rapidly scanned, so that heat can be generated in the targets before much thermal diffusion to surrounding tissues can occur.

For example, dermal microvessels can be selectively damaged by irradiation with a wavelength that passes well through the overlying epidermis and is then strongly absorbed by blood in the underlying dermal vessels. The chief visible chromophores (pigments) in blood are hemoglobins and bilirubin; in the epidermis, melanin is the major chromophore (see Fig. 1). Oxyhemoglobin has absorption peaks at 418, 540, and 577 nm. Melanin absorption and dermal scattering at 418 nm [32] are quite strong, but decrease at longer wavelengths. The sequelae of melanin absorption is damage to melanin-containing epidermal cells, which is undesirable for the goal of selective vascular injury. The longer wavelength 577 nm light is less strongly absorbed by melanin and less strongly scattered within the dermis, however, and therefore represents a wavelength at which dermal vessels can be selectively damaged without significant epidermal injury in Caucasians [1].

To maximally confine the deposited energy within the targeted structure (the microvessels), one must choose an exposure duration less than or about equal to the target thermal relaxation time, τ_R. Table 2 gives approximate thermal relaxation times for biologic structures of various sizes. The ectatic cutaneous vessels found in port wine stains (PWS) [33] are typically about 35 μm in diameter. In PWS patients, these abnormal superficial vessels cause the red to violet color of these "birthmarks" and can be markedly disfiguring. A pulse duration of less than 1 msec confines selectively absorbed laser energy within these vessels and, hence, a 577 nm laser exposure of 1 msec or less may be ideal for selective treatment of PWS lesions. On the other hand, pulse durations less than about 10 μsec should confine the thermal energy to the erythrocytes, the cells in which all oxyhemoglobin normally occurs. For these short pulse durations, violent erythrocyte rupture and resultant mechanical vessel wall damage appears to occur. Exposure or pulse durations of longer than about 20 μsec therefore may be preferable to avoid hemorrhage, yet still damage the abnormal vessels of PWS lesions.

Experimental verification of the above theoretical predictions was obtained in a series of studies. By irradiating normal human forearm skin with 300 nsec (0.3 μsec) pulse duration, 577 nm wavelength light from a dye laser [34], the light-microscopic histologic alterations in Caucasian skin were limited to vascular structures, particularly the superficial venous plexus (SVP). At 590 nm, a wavelength only 13 nm away

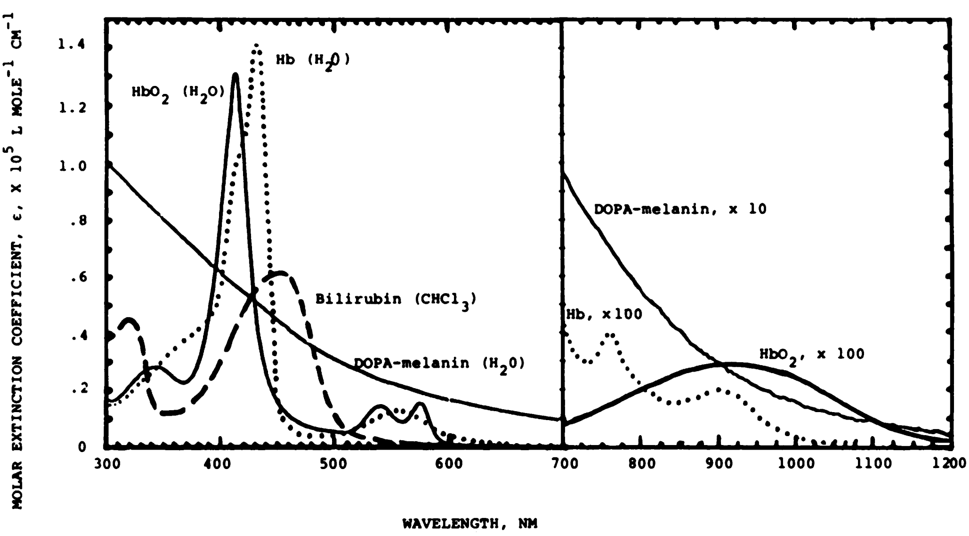

FIG. 1. The absorption spectra of hemoglobin, oxyhemoglobin, melanin, and bilirubin; solvent indicated in parentheses. Note that for wavelengths greater than 700 nm, the scale change for DOPA-melanin is ×10, while for Hb and HbO_2 it is ×100. Selective photothermolysis of cutaneous blood vessels is possible at a wavelength that is relatively well-absorbed by blood constituents (e.g., HbO_2) but is poorly absorbed by structures that intervene between the light source and the vessels (e.g., melanin).

from 577 nm but much less strongly absorbed by blood, no vascular changes were observed, confirming the primary role of oxyhemoglobin absorption. Using an *in vivo* hamster cheek pouch model, vessels could be directly observed during 577 nm, 300 nsec irradiation [1]. As the radiant exposure dose is increased, hemoglobin denaturation and protein coagulation, then hemostasis, and finally vessel rupture occur. As discussed above, the short pulse duration appears to cause violent erythrocyte rupture and vessel wall damage. A subsequent study in humans comparing 1.5, 10, 56, 200, and 360 μsec, 577 nm pulses [35] supports the role of pulse duration in controlling vessel rupture, as expected. Histologic evidence indicates that pulses shorter than 20 μsec cause erythrocyte and vessel wall rupture with subsequent hemorrhage into the surrounding dermis. The longer pulses heat the entire vessel, causing coagulation and irreversible but selective vascular damage without apparent vessel rupture.

Selective photothermolysis is based upon achieving a damaging temperature in target structures via a photon-induced temperature rise. Thus, more laser energy should be needed to reach this damaging temperature if the ambient tissue tempera-

TABLE 2
The Thermal Relaxation Time of Various-Sized Structures

Radius (μm)	τ_R	Structure
1	2.5 μsec	Mitochondrian
3	23 μsec	Red blood cell
7	120 μsec	Capillary
10	250 μsec	Arteriole
15	560 μsec	Venule
35	3 msec	Ectatic vessel

ture is lowered. Indeed, at a skin temperature of 20°C, a larger radiant exposure (1.50 J/cm^2) was needed to induce purpura than at 33°C (1.29 J/cm^2) [36].

The above research is the basis for an improved laser treatment of port wine stains (PWS), a congenital abnormal collection of ectatic dermal vessels. Port wine stains have been treated with several lasers; namely, the ruby [37], CO_2 [38], and argon [39]. Treatment with each of these lasers can lead, however, to unacceptable scarring because of generalized epidermal and dermal damage. Using a dye laser emitting a 577 nm one-millisecond or shorter pulse of light, improved cosmetic results might be expected, as previously discussed [40]. Initial studies with 1 μsec pulses were poor, probably because of the hemorrhage induced by these short pulses [41]. Compared with conventional argon or CO_2 laser therapy, however, very encouraging results have been seen in PWS patients treated with 360 μsec pulses [42]. No scarring was noted, and clearance of the irradiated area was observed in six weeks without the epidermal damage or wound care required with other lasers.

When vessel destruction is desired, hemoglobin is not always on appropriate target chromophore because other overlying chromophores may compete too strongly for absorption. For example, in the retina, absorption by melanin in the retinal pigment epithelium (RPE) and macular pigments limits the potential of selectively targeting the neovascularization that occurs in senile macular degeneration [43]. Laser treatment with, for example, a krypton laser (red line at 647 nm) [43,44] appears to limit choroidal neovascularization, but also produces a permanent scotoma by destruction of the overlying RPE and neural retina. Light at 577 nm is also too strongly absorbed by the RPE to avoid scotomas, and, at present, foveal lesions invariably lead to central blindness. A potential solution is to inject an exogenous chromophore into the blood, i.e., a stable non-toxic dye, that has a strong absorption where the RPE and macular pigments have weak absorption. Such a spectral region exists in the near-infrared.

The potential feasibility of using this near-infrared exogenous chromophore approach was demonstrated *in vivo* in albino rabbit eyes [45], using a 694 nm pulsed ruby laser, and indocyanine green as the exogenous chromophore. Indocyanine green, currently used clinically for the indicator dilution method determination of cardiac output, has a broad absorption peak near 805 nm and binds together to albumin, thus remaining intravascular. The ruby laser light is strongly absorbed in the short-wavelength tail of the dye's absorption band. Other, near infrared lasers—for example, the erbium laser—are probably better suited to optimize this potential new treatment modality for possible use in patients.

Another example of selective photothermolysis is the selected targeting of melanosomes with laser pulses less than 1 μsec in duration, at wavelengths selectively absorbed by melanin. Skin of normal human volunteers was exposed to 20 nsec pulses from a xenon fluoride (XeF) excimer laser (351 nm wavelength) [25]. For radiant exposures greater than 0.12 J/cm^2, there was disruption of the melanosomes within melanocytes and basal keratinocytes by electron microscopy. Biopsies at 24 hours showed subsequent degeneration of these melanin-containing cells. Langerhans cells, and other nonmelanin-containing epidermal cells were unaltered. Thus, selective thermolysis of pigmented organelles and single cells within tissue is possible.

Thus far, several exogenous chromophore systems have been discussed (carotenoids, indocyanine green) for thermally mediated selective photothermolysis or ablation. Photochemically mediated damage, however, offers a greater range of possible exogenously targetted phototoxic effects. One such scheme involves delivering phototoxic chromophore to the site of interest via linkage to monoclonal antibodies (MAb's). Hematoporphyrin (HP) diahydiazide has been linked to the oxidized carbohydrate moiety on the Fc region of anti-T cell MAb's. MAb binding specificity and HP singlet oxygen production were unaffected, with conjugation ratios between 0.85 and 3.0 HP/MAb. The killing of both leukemia and stimulated T cells was both light dose and HP concentration dependent [47,48] and specific to the cells targeted by the MAb. The mechanism of cell killing in these studies probably involves singlet oxygen production.

CONCLUSIONS

A few of the basic mechanisms of laser-tissue interactions have been presented. The number of potential therapies is large; however, laser medicine is still in its infancy. Of the hundreds of lasers now available, only a few are used for therapy, mainly because our understanding of basic laser-tissue interactions is limited. Elucidation of these interactions is difficult, requiring expertise from a wide variety of disciplines including engineering, physics, chemistry, immunology, and an array of medical specialties. Sophisticated lasers and other technology are also required. The biologic effects of many laser-tissue interactions are poorly understood but certainly open to careful study. Already the benefits of such collaborative research are being seen. Port wine stains and pigmented skin lesions may be better treated using selective photothermolysis, as discussed. We now have femtosecond (10^{-15} seconds) ranging techniques for accurate *in vivo* diagnosis of ocular pathology [49], and doppler shift measurements of capillary blood flow [50]. Recently, *in vivo* fragmentation/ablation of urinary calculi (calcium oxalate stones) was demonstrated, using a dye laser tuned to 450 nm with a one-microsecond pulse duration [51]. Other research will enhance *in vivo* spectroscopy and potentially lead to the development of "smart lasers," in which the laser parameters (e.g., pulse duration) are controlled by a fast diagnostic feedback system.

The financial cost of laser research may be initially high; however, the potential to improve patient care is immense; the prospect of changing expensive, high-morbidity, invasive, inpatient surgical operations into less expensive, low morbidity, non-invasive, outpatient procedures is in the best interest of patient and physician alike.

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